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(54) **Use of thiazolidine-4-carboxylate derivatives and glutathione esters for the treatment of pulmonary diseases.**

(57) The present invention provides for the preparation of a composition used for treating pulmonary disease. More specifically, the present invention provides for the preparation of a composition for treating diseases such as adult respiratory distress syndrome which result in oxidative stress that damages the cells of the lung. Pursuant to present invention, a non-cysteine substrate that is a precursor for the intracellular synthesis of glutathione is used to create a composition that is administered to a patient and increases the intracellular glutathione levels of at least the cells of the lungs of a patient with pulmonary disease.

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BACKGROUND OF THE INVENTION

The present invention relates generally to the treatment of pulmonary disease. More specifically, the present invention relates to the preparation of compositions that can be used for the treatment of diseases that result in acute and/or chronic respiratory distress.

There are a number of pulmonary or respiratory disease states that can cause acute or chronic respiratory distress and result in damage to the lungs of the patient. Resulting damage can be debilitating to the patient and on occasion result in death.

Adult respiratory distress syndrome (ARDS) is a common medical emergency that is precipitated by a variety of acute processes that directly or indirectly injure the lungs. For example, ARDS can be precipitated by primary bacterial or viral pneumonias, aspiration of gastric contents, direct chest trauma, prolonged or profound shock, burns, near drowning, fat embolism, blood transfusions, cardio-pulmonary bypass, O₂ toxicity, or acute hemorrhagic pancreatitis. ARDS usually develops within twenty-four to forty-eight hours after initial injury or illness. It is believed that activated leukocytes and platelets accumulate in the capillaries, interstitium, and airspaces. They may release products including prostaglandins, toxic O₂ radicals, proteolytic enzymes, and other mediators that injure cells, promote fibrosis, and alter bronchomotor tone and vasoreactivity. See, The Merck Manual, Fifteenth Edition.

Injury to the pulmonary capillary endothelium and alveolar epithelium causes plasma and blood to leak into the interstitial and intra-alveolar spaces. Flooding of the alveolae and atelectasis results. Typically, within two or three days, a second phase of lung injury is characterized by bronchoalveolar inflation. Additionally, there is proliferation of epithelial and interstitial cells. Typically, in a third phase collagen accumulation may progress rapidly. This can result in severe interstitial fibrosis within two to three weeks. This pathological change, can lead to low lung compliance, pulmonary hypertension, decreased functional residual capacity, ventilation/perfusion maldistribution, and hypoxemia.

Unfortunately, the survival rate for severe ARDS is less than 50% with appropriate treatment. Although the mechanism of lung injury in adult respiratory distress syndrome is not certain, data from animal models and indirect evidence from studies in human beings has suggested that toxic oxygen metabolites produced by stimulated neutrophils are a possible agent of the alveolar injury. Baldwin, et al, Oxidant Activity In Expired Breath of Patients With Adult Respiratory Distress Syndrome, The Lancet, January 4, 1986, pages 11-13.

Because it has been hypothesized that oxygen free radicals released during endotoxemia may contribute to the lung injury of ARDS, the effect of intravenous n-acetylcysteine, a free radical scavenger, on the endotoxin induced model of ARDS in awake sheep has been investigated. Bernard, et al., Effect of N-acetylcysteine on the Pulmonary Response to Endotoxin in the Awake Sheep and Upon In Vitro Granulocyte Function, J. Clin. Invest., Vol. 73, pp 1772-84 (1984). The paper states that n-acetylcysteine inhibits granulocyte aggregation and scavenges free radicals in vitro. The paper postulates, therefore, that the beneficial effect of n-acetylcysteine in attenuating the pathophysiologic processes seen in the sheep model of the adult respiratory syndrome is due to its ability to scavenge oxygen free radicals in vivo.

Lucht, et al., Prevention of Release of Granulocyte Aggregants Into Sheep Lung Lymph Following Endotoxemia By Acetylcysteine, The American Journal of the Medical Sciences, Vol. 294 No. 3 (September 1987), discusses experiments wherein n-acetylcysteine was administered to sheep before endotoxin infusion. The paper concludes that endotoxemia causes the release from the lungs of substance(s) that activate granulocytes, and that this response is prevented by n-acetylcysteine, possibly as a result of the antioxidant properties of the drug.

Although, attention has focused on treating and/or curing ARDS, an effective treatment is still not available.

Infant respiratory distress syndrome, or IRDS, is a disorder primarily of prematurity, manifested clinically by respiratory distress and pathologically by pulmonary hyaline membrane disease and atelectasis. See Merck Manual, Fifteenth Edition. IRDS results from diffuse lung atelectasis due to a deficiency of pulmonary surfactants at birth. Due to pulmonary insufficiency, these neonates are placed in hyperoxic (95% O₂) environments. The inability to produce adequate amounts of glutathione exacerbates the oxidative stress and damage to the lungs. If untreated, IRDS can result in bronchopulmonary dysplasia, blindness, brain damage, multiple organ failure and death.

Other disease states, such as cystic fibrosis, idiopathic pulmonary fibrosis, and emphysema, also can result in lung damage due to cell damage from oxidation. The lungs are exposed to oxidative stress due to airborne oxidants and to hyperoxygen stress when respiratory treatment includes elevated oxygen (e.g., 95% O₂) treatment. Additionally, inflammatory cells, macrophages, neutrophils, and the like, secrete active oxygen species in the lungs.

SUMMARY OF THE INVENTION

The present invention relates to a method for treating pulmonary disease. Specifically, the present invention relates to a method for treating pulmonary disease by increasing the intracellular synthesis of glutathione. To this end, pursuant to the present invention, a non-cysteine glutathione precursor is used in the manufacture of a composition that is administered to a patient to treat pulmonary disease.

It has been found, that by increasing glutathione levels within a cell, the pulmonary cells will experience reduced damage when exposed to oxidative stress. Cells having depressed glutathione levels are susceptible to membrane lipid peroxidation, mitochondrial damage, and progressive fibrosis of lung tissue. However, turnover of glutathione and of endogenous antioxidants in pulmonary endothelium is very rapid.

In an embodiment of the present invention, L-2-oxothiazolidine-4-carboxylate is utilized to elevate tissue glutathione levels. In another embodiment, glutathione esters are utilized to elevate glutathione levels within the cells.

In a further embodiment of the invention, the present invention provides for the use of non-cysteine substrates to create a composition that is used to treat adult respiratory distress syndrome by being administered to a patient having adult respiratory stress syndrome, in a sufficient amount to elevate the intracellular level of glutathione, at least in the lungs, of a patient.

In an embodiment, the non-cysteine substrate is administered parenterally.

In an embodiment of the present invention, the non-cysteine substrate is administered enterally.

Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention provides for the use of a non-cysteine precursor to create a composition for treating pulmonary disease. More specifically, the present invention provides a composition that can be used for treating diseases such as adult respiratory distress syndrome and infant respiratory distress syndrome which result in oxidative stress that can damage the cells of the lung.

Pursuant to the present invention, a composition is provided that increases the intracellular glutathione levels of at least the cells of the lungs of a patient with pulmonary disease. It has been found that in acute respiratory distress syndromes glutathione levels of many patients are suppressed. Due to the suppressed levels of glutathione, oxidative stress can occur that damages the lung cells.

Pursuant to the present invention, a non-cysteine substrate that is a precursor for the intracellular synthesis of glutathione is administered to the patient. Because the substrate is not a cysteine substrate, a more effective tissue distribution of the substrate occurs within the patient. It is believed that the enzymes necessary for deacetylation of an acetylated compound such as n-acetylcysteine exist only in the kidney. Accordingly, a compound such as n-acetylcysteine must be metabolized to cysteine in the kidney then transported to the liver or peripheral cells. Therefore, such compounds may not be sufficiently distributed to the requisite tissues of the patient, i.e., the tissue of the lungs.

Furthermore, because the present invention provides a non-cysteine substrate the compound is not itself an anti-oxidant. Although it may be desirable to introduce an anti-oxidant into a patient having adult respiratory distress syndrome to prevent damage from the oxygen radicals, anti-oxidants are not stable.

Pursuant to the present invention any non-cysteine substrate that stimulates intracellular glutathione synthesis can be utilized. Preferably, the method comprises the step of administering an agent chosen from the group consisting of L-2-oxothiazolidine-4-carboxylate and glutathione esters. However, other thiazolidine-4-carboxylate analogs that are converted intracellularly to glutathione can be utilized.

L-2-oxothiazolidine-4-carboxylate, in vitro, is subjected to the action of 5-oxo-L-prolinase in the presence of adenosine triphosphate to produce S-carboxyl cysteine. S-carboxyl cysteine is then decarboxylated to produce cysteine. Cysteine is then metabolized to provide glutathione. See, U.S. Patent Nos.: 4,335,210; 4,434,158; 4,438,124; 4,665,082; and 4,647,571 the disclosures of which are incorporated herein by reference.

As previously stated, the non-cysteine substrate can include a glutathione ester. For example, the compound can have the structure:



wherein R is an alkyl group containing 1 to 10 carbon atoms. Preferably, the methyl and ethyl glutathione esters are used. It is also preferred to use glutathione isopropyl ester. Glutathione esters are disclosed in U.S. Patent No. 4,784,685, the disclosure of which is incorporated herein by reference.

In an embodiment of the invention, the composition of the present invention includes: 3% L-2-oxothiazolidine-4-carboxylate in a phosphate buffer. Additional embodiments include:

- a) A buffered (pH 6.5 - 6.8) 3% or 6% L-2-oxothiazolidine-4-carboxylate or glutathione ester aqueous solution.
- b) A buffered 3% or 6% L-2-oxothiazolidine-4-carboxylate or glutathione ester aqueous solution containing any of the following, alone or in appropriate combinations: amino acids, dextrose or other carbohydrate sources, and lipid emulsions.
- c) A vial containing a crystalline or lyophilized non-cysteine glutathione precursor to which appropriate aqueous solutions are added at time of use.
- d) A gelatin capsule containing a crystalline or lyophilized non-cysteine glutathione precursor.
- e) A pill containing a crystalline or lyophilized non-cysteine glutathione precursor.
- f) A liquid elemental, protein hydrolysate, carbohydrate and/or lipid emulsion containing enteral dietary supplement containing a non-cysteine glutathione precursor.

The composition can be administered as an adjunct therapy with other typical therapies. For example, steroids, non-steroid anti-inflammatories, prostaglandin synthesis inhibitors (ibuprofen), mucolytics, tumor necrosis factor antibodies, artificial surfactants (Exosurf, Surventa), hyperoxic and ventilation therapies, and antibiotics can be administered with the present invention.

By way of example, but not limitation, contemplated examples of the present invention will now be given.

EXAMPLE 1

A 55-year-old patient with sepsis syndrome that progressed into ARDS was given an intravenous administration of a neutral (pH 6.5 - 6.8) 6% solution of L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. for 10 days. It should be noted that a continuous infusion of a 6% solution equivalent to 45 mg/kg/day could have been used as an alternative dosing regimen. The infusion although by independent intravenous administration, could have been through an indwelling intravenous catheter.

The patient demonstrated the following physiological characteristics at the start and end of treatment:

Physiology	Start	End
PaO ₂ /PAO ₂	0.24	0.38
Cardiac Output (liters/min)	5.65	7.93
Thoracic Static Compliance 20(ml/cm H ₂ O)	34.4	42.3
Chest Radiograph of Pulmonary Edema (0 = normal, 3 = severe)	2.5	1.1
Plasma Glutathione (nmoles/ml)	2.47	7.96
Red Cell Glutathione (nmoles/ml)	2,753	5,825
Lung Glutathione (nmoles/ml by Bronchoalveolar lavage)	84	398

EXAMPLE 2

A neonate born at 27 weeks gestational age, weighing 984 grams, and suffering from Hyaline membrane disease was placed in a ventilator and given Exosurf (95cc/kg) at 18 and 30 hrs of age. The patient received an intravenous administration of a neutral (pH 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d., as a continuous infusion. A 6% solution equivalent to 45 mg/kg could have also been administered. The administration was continued until the infant has sufficiently developed to demonstrate adequate blood oxygenation in a normoxic environment, without mechanical or artificial ventilatory support.

The neonate displayed the following ventilatory requirements at entry and at 28 days:

	Entry	Day 28
Oxygenation index	1.48	0.62
Ventilation rate	920/24hr	223
FiO ₂	1184/24hr	774
Positive end-expiratory pressure	104/24hr	31
Mean airway pressure	208/24hr	56

(Values are summation of area under curve for 24 hour measurements).

At 28 days the patient was scored 1.5 for bronchopulmonary dysplasia, 1.0 for retrolental fibroplasia and 0.5 for intraventricular hemorrhage on a 0 to 5 scale (0 being normal, 5 being severe).

EXAMPLE 3

An 18-year-old hospitalized cystic fibrosis patient received intravenous tobramycin and ceftazidime every eight hours for 6 days. The patient received an intravenous administration of a neutral (pH 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. during continuous infusion. Alternatively, a 6% solution equivalent could have been administered. Although administration occurred during in-patient treatment it could have occurred using home intravenous drug therapy. Administration of the non-cysteine glutathione precursor occurred by independent injection at infusion, but could have taken place by infusion through an indwelling intravenous catheter.

The following changes in physiological characteristics were recorded at termination of treatment;

SaO ₂	+3.6%
Weight (% increase)	+4.5%
FVC (%predicted)	+15.9%
FEV1 (% predicted)	+14.3%
Bronchoalveolar lavage glutathione	+322%

The patient with cystic fibrosis also receive an enteral dose of the non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., as a prophylactic treatment during periods free of acute respiratory infection. The enteral dose was given as a capsule, but could have been given as a pill, liquid, or as part of a nutrient containing liquid enteral diet, or as a combination of these delivery methods.

EXAMPLE 4

A 68-year-old malnourished patient with an acute exacerbation of emphysema is admitted to the respiratory ICU. The patient requires mechanical ventilation and nutritional support. An enteral diet containing 18% protein, 27% CHO, 55 fat is provided at 1.3 times the resting energy expenditure. The diet was supplemented with 15 mg/kg of a non-cysteine glutathione precursor in 250 ml of diet. The patient was successfully weaned from the ventilator and diet on day 8. Lung lavage glutathione levels were taken at admission and on day 7:

	Admission	Day 7
PaCO ₂	6.09	5.15
PaCO ₂ /PAO ₂	31.5	38.4
Ventilation rate (b/m)	31	24
Minute volume (l/m)	16.5	14.2
Glutathione (umol/ml)	95	402

It is anticipated that a patient with emphysema would receive an enteral dose of a non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., during periods of acute exacerbations, and as a prophylactic treatment during quiescent periods. The enteral dose could be given as a capsule, pill, liquid, or as part of a nutrient containing liquid enteral diet, or as a combination of these delivery methods.

It should be understood that various changes and modifications to the presently preferred embodiments

described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

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Claims

1. Use of a non-cysteine substrate that stimulates the intracellular synthesis of glutathione for the preparation of a composition for treating pulmonary disease in a patient suffering from same the non-cysteine substrate being administered to a patient in an amount sufficient to increase intracellular glutathione levels of at least the lung cells.
2. The use of a compound chosen from the group consisting of: L-2-oxothiazolidine-4-carboxylate; glutathione ester; and thiazolidine-4-carboxylate analogs, for creating a composition for treating a respiratory distress syndrome the composition being administered to a patient having a respiratory distress syndrome in an amount sufficient to stimulate intracellular glutathione synthesis.
3. The use of a non-cysteine substrate that stimulates the intracellular synthesis of glutathione for reducing oxidative damage to lung tissue in a patient, the composition being administered to a patient likely to suffer oxidative damage to lung tissue in an amount sufficient to increase the intracellular level of glutathione in lung tissue.
4. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is administered parenterally.
5. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is administered enterally.
6. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is L-2-oxothiazolidine-4-carboxylate.
7. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is a glutathione ester.
8. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is a thiazolidine-4-carboxylate analog.
9. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is a methyl ester of glutathione.
10. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is an ethyl ester of glutathione.
11. The use according to Claims 1, 2, or 3 wherein the non-cysteine substrate is a glutathione isopropyl ester.
12. The use according to Claims 1, 2, or 3 wherein the patient has adult respiratory distress syndrome.
13. The use according to Claim 1, 2, or 3 wherein the patient has infant respiratory distress syndrome.
14. The use according to Claims 1 or 3 wherein the patient has cystic fibrosis.
15. The use according to Claims 1 or 3 wherein the patient has emphysema.
16. The use according to Claims 1 or 3 wherein the patient has idiopathic pulmonary fibrosis.

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(54) **Use of thiazolidine-4-carboxylate derivatives and glutathione esters for the treatment of pulmonary diseases.**

(57) The present invention provides for the preparation of a composition used for treating pulmonary disease. More specifically, the present invention provides for the preparation of a composition for treating diseases such as adult respiratory distress syndrome which result in oxidative stress that damages the cells of the lung. Pursuant to present invention, a non-cysteine substrate that is a precursor for the intracellular synthesis of glutathione is used to create a composition that is administered to a patient and increases the intracellular glutathione levels of at least the cells of the lungs of a patient with pulmonary disease.

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EUROPEAN SEARCH REPORT

Application Number

EP 91 12 1524

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 127, no. 1, 28th February 1985, pages 270-276, Academic Press, Inc.; M.-F. TSAN et al.: "Enhancement of intracellular glutathione protects endothelial cells against oxidant damage" * Whole document, especially: "Discussion" * ---	1,2,3,6 ,12	A 61 K 31/425 A 61 K 37/02
X	INFLAMMATION, vol. 12, no. 2, 1988, pages 113-121, Plenum Publishing Corp.; M.-F. TSAN et al.: "L-2-oxothiazolidine-4-carboxylate protects cultured endothelial cells against hyperoxia-induced injury" * Paragraph: "Discussion" * ---	1,2,3,6	
X	AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, vol. 2, no. 1, January 1990, pages 81-90; P.H.S. SPORN et al.: "Complex effects of In Vitro hyperoxia on alveolar macrophage arachidonic acid metabolism" * Paragraph: "Discussion" * ---	1,2,3,6	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K
X	AM. REV. RESPIR. DIS., vol. 133, 1986, page A395; M.A. PASSERO et al.: "L-2-oxothiazolidine-4-carboxylic acid increases glutathione in mouse lung" * Whole document * ---	1-4,6	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 19-08-1992	Examiner KLAVER T.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document			

EPO FORM 1503 (03.92) (P/0401)



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.
- namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

See sheet -B-

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
- namely claims:
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.
- namely claims:



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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	BIOCHEMICAL PHARMACOLOGY, vol. 39, no. 12, 1990, Pergamon Press plc, GB, pages 1877-1881; S. UHLIG et al.: "Glutathione enhancement in various mouse organs and protection by glutathione isopropyl ester against liver injury" * Pages 1878-1879 * -----	1-4,7, 11	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	19-08-1992	KLAVER T.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application I : document cited for other reasons & : member of the same patent family, corresponding document			

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EP 91 12 1524 -B-

LACK OF UNITY OF INVENTION A POSTERIORI

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1,3-6,8,12-16 and 2 partially: Use of L2-oxothiazolidine-4-carboxylate to treat pulmonary diseases.
2. Claims 7,9,10,11 and 2 partially: Use of a glutathione ester to treat pulmonary diseases.